Atlas of Genetics and Cytogenetics in Oncology and Haematology

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Gene Section

Review

FZD4 (frizzled class receptor 4)

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Abstract

Fzd4 is a receptor for Wnt proteins, belonging to the frizzled receptors family. Its stimulation can activate both Wnt/β-catenin canonical and Wnt/Ca^{2+} non canonical pathways. This receptor plays an important role in the development processes, in particular in the retinal vascularization: it binds the Norrin ligand, a Wnt-unrelated growth factor, and activates β-catenin signalling pathway. Mutations of FZD4 gene are associated with Familial Exudative Vitreoretinopathy (FEVR). Recently dysregulation of FZD4 expression has been reported in different type of cancers, but FZD4 contribution in tumor pathogenesis and progression is still not entirely elucidated.

Keywords
Frizzled 4, WNT, Wnt/β-catenin signaling

Identity

Other names
Frizzled 4, Seven Transmembrane Spanning Receptor, Frizzled (Drosophila) homology 4, Frizzled homolog 4 (Drosophila), CD344 Antigen, FEVR, Fz-4, FZD4, Wnt receptor Frizzled -4, hFz4

HGNC (Hugo)
FZD4

Location
11q14.2

Location (base pair)
Starts at 86945675 and ends at 86955398 bp from pter (according to hg38-Dec_2013)

DNA/RNA

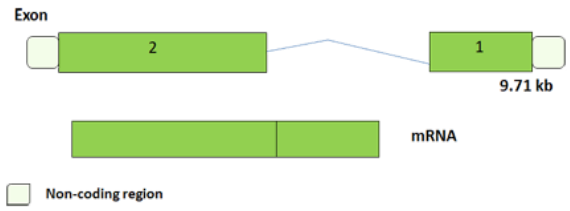


Figure 1: Schematic representation of FZD4 gene that contains a total of two exons and FZD4 transcript.

Description

DNA size: 9.71kb encoding two exons. This gene has one transcript (splice variant), 82 orthologues, 12 paralogues (www.emsable.org). Sagara et al., reported a splice variant of FZD4 gene which they called FZD4SA, it retains intronic sequence and encodes shorter isoform of only 125 aa. However, its expression is not supported by other experimental evidences.

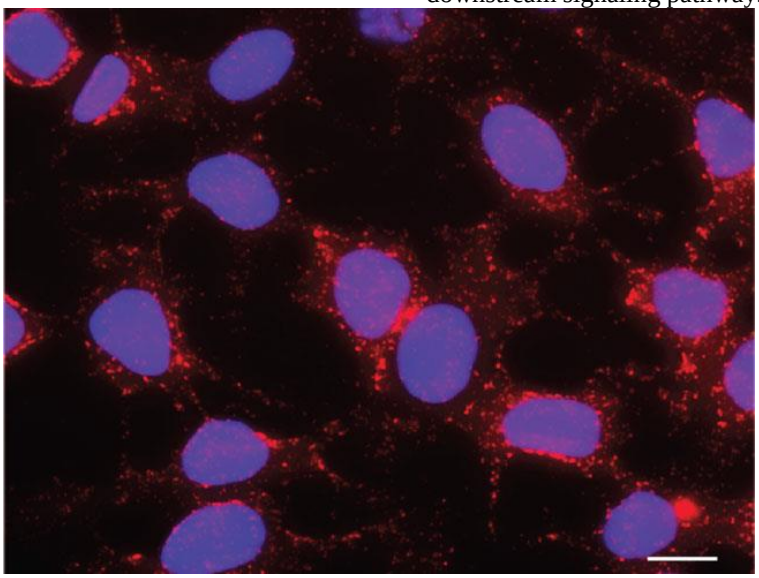
Transcription

The FZD4 mRNA transcript is 7383 bp. FZD4-001 ENST00000531380.1: mRNA7383 bp, protein 537 aa.

Protein

Description

The gene FZD4 encodes a 537 aa protein with a molecular weight of 59 kDa. FZD4 is a member of the seven transmembrane receptor family consist of 10 receptors that are activated by Wnt family of lipo-glycoproteins. The Wnt/ FZD signaling is involved in a variety of biological processes and its dysregulation have been implicated in cancer development. FZD4 protein contains the N-terminal signal peptide (aa 1-36) that assurances proper membrane insertion of the protein, an extracellular cysteine rich domain (CRD; aa 40-161), which creates the binding site for WNT ligands, a seven-pass transmembrane domain (aa 161-221) that gives rise to three intracellular loops, three extracellular loops and a C- terminal domain (aa 221-537). The CRD domain is necessary to bind WNT ligands or Norrin ligand leading to initiation of distinct downstream signaling pathways. (Schulte G., 2010).



Expression

In human, FZD4 is a ubiquitous protein. It is expressed in brain, ovary, liver, pancreas, brain, colon, heart, skeletal muscle, endothelial cells, endometrium, bone marrow, prostate, spleen, breast (www.ncbi.nlm.nih.gov).

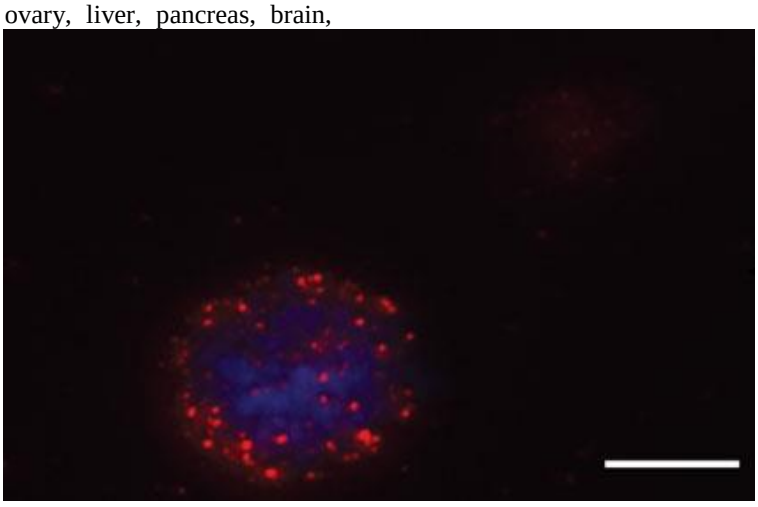
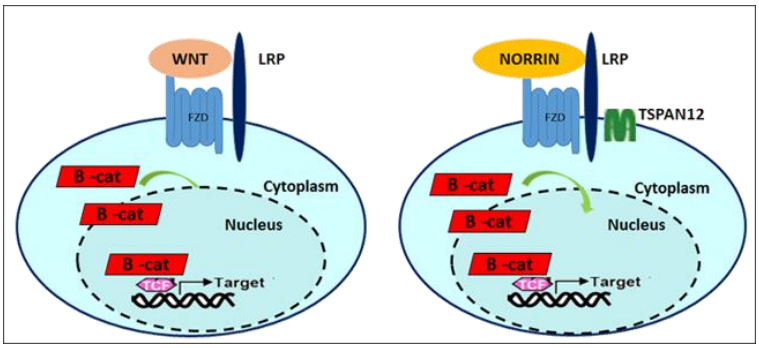


Figure 3: Visualization of FZD4/WNT10B interaction in MCF7 adherent (top) and tumorsphere (bottom) by proximity ligation assay (Lazzaroni et al.,2016).

Localisation

FZD4 is localized on the plasma membrane surface. It can be internalized through both constitutive and agonist dependent endocytosis in response to Wnt5a stimulation (Chen W. et al., 2003).



Function

FZD4 is a member of Frizzled gene family involved in neuronal, follicle, cardiomyocyte and retinal vascular development, likewise its dysregulated expression lead to cancer and other diseases. Depending on the cellular contest, FZD4 interacts with different WNT ligands, leading to the activation of Wnt/β catenin signaling and sometimes non canonical Wnt/Ca^{2+} signaling. Wnt/β catenin signaling is activated when WNT ligands bind CDR FZD/Low-density lipoprotein receptor-related protein5/6 (LRP5/ LRP6) complex, in this case CTNNB1 (β-catenin) degradation complex becomes inactivated, resulting in stabilization of β-catenin that can translocate in the nucleus, where it interacts with LEF1 (TCF/LEF) transcription factor, inducing the transcription of target genes (Clevers H., 2006). Recently, WNT10B/FZD4 interaction in the MCF7 breast cancer cell line suggests an autocrine activation of Wnt signalling in this cell line model (Lazzaroni F. et al, 2016). In melanoma FZD4 binds WNT5A and stimulates tumor invasion through activation of βcatenin signaling (Grossman A. et al., 2013), while in acute myeloid leukemia the interaction between WNT3A and FZD4 induce higher resistance against apoptosis (Tickenbrock L. et al., 2008). WNT2, WNT5A/ WNT5B and WNT11 via FZD4 and FZD6 induced non canonical Wnt signaling activation that regulates cardiomyocite differentiation (Mazzotta S. et al., 2016)
FZD4 is also the only FZD family member that binds selectively a growth factor called NDP (Norrin) and regulates endothelial cells growth during retinal vascular development. In retina, the binding of Norrin with FZD4 conjugated with LRP5 co-receptor and protein TSPAN12 (Tetraspanin-12), results in activation of βcatenin signalling (Schulte G., 2010), alteration in one of this gene is associated with Familial Exudative Vitreoretinopathy.

Homology

The FZD4 gene is conserved in chimpanzee, mouse, Rhesus monkey, dog, cow, rat, chicken, zebrafish and frog.

Mutations

Germinal

Several types of mutations (missense, nonsense, small deletions) have been reported for the human FZD4 gene and are related to the familial exudative vitreoretinopathy (FEVR). Among these mutations, different heterozygous substitutions have been reported: M342V, W335C, R417, I256V, P33S, G36N, H69Y, M105T, M105V, C181R, C204R, C204Y, C45Y, Y58C, W226X, and G488D (Zhang K. et al., 2011; Kondo H. et al. 2003; Quin et al., 2005) It has also been described a loss of function mutation of FZD4 with nucleotides 1479-1484 deletion in two cases of FEVR, resulting in the lacking of met493 and trp494 that leads to a frameshift and creates a stop codon at residue 533 (Robitaille J. et al.,2002).

Implicated in

Familial Exudative Vitreoretinopathy (FEVR)

Familial Exudative Vitreoretinopathy (FEVR) is a hereditary ocular disorder characterized by incomplete development of the retinal vasculature.

It is possible to distinguish two forms of FEVR: one with dominant autosomal inheritance and one with X-linked recessive inheritance (Gilmour DF., 2015).

Autosomal inheritance has been associated with mutation of FZD4, LRP5 or Tetraspanin 12 (TSPAN12) genes, while X-linked recessive inheritance is due to mutation of Norrin gene (NPD) that it is also involved in other ocular disease.

Several FZD4 mutations were connected with FEVR, many of which were found in the extracellular portion of the protein. Kaykas et al., have shown how some FZD4 mutations in FEVR lead to the retention of mutated protein within the endoplasmic reticulum (ER), where it is recognized by endoplasmic-reticulum-associated protein degradation (ERAD) and degraded, not allowing its exposure on the plasma membrane. They also demonstrated that oligomerization of mutants and wild-type FZD4 in the ER reduces the FZD4 function by preventing a sufficient amount of FZD4 from reaching the cell membrane and inhibits its

signaling. This dominant-negative effect can partly explain the pathological mechanism that causes the disease phenotype, in patients with heterozygous FZD4 mutations. Mutations that do not cause retention in ER of mutated protein, induce a conformational modification of the CRD FZD4 that doesn't permit the biding to its ligands or downstream targets.

Acute myeloid leukemia (AML)

It was demonstrated that FZD4 represents one of the mechanism of canonical or non canonical Wnt signaling activation in the pathogenesis of AML. Recently microarray analysis confirmed a higher expression of FZD4 in primary AML blast cells. (Beghini A. et al., 2012).

Tickenbrock, A. et al, also showed FZD4 overexpression in primary AML blasts, both in the presence or absence of FLT3 mutations. They also showed a canonical Wnt pathway activation due at specific WNT3A/FZD4 interaction, that leads to the stabilization of β-catenin and induces higher resistance against apoptosis. It was observed an involvement of FZD4 in differentiation of AML cell line mediated by 6-benzylthioinosine (6-BT) treatment. 6-BT treatment results in downregulation of canonical Wnt molecules and up-regulation of transcriptional level of the non canonical Wnt ligand Wnt5a and receptors FZD2, FZD4, FZD5, resulting in activation of Wnt/Ca^{2+} pathway (Zang S. et al., 2014).

Non small cell lung cancer (NSCLC)

Recently several studies have reported that single nucleotide polymorphisms (SNPs) of FZD4 gene can influence recurrence and survival of early stage NSCLC patients treated with only surgery or in combination with chemotherapy.

miR-related SNP (rs713065) in the 3?UTR region of FZD4 gene is associated with decreased risk of death in early stage NSCLC patients treated with only surgery, while it is related to increased risk of death in patients treated with surgery plus chemotherapy (Pu X. et al., 2013). This FZD4-miR-SNP specifically interacts with MIR204 which acts as a tumor suppressor and inhibits the expression of FZD4 and transduction of Wnt/βcatenin signalling (Lin J. et al, 2017).) This FZD4-miR-SNP specifically interacts with miR-204 which acts as a tumor suppressor and inhibits the expression of FZD4 and transduction of Wnt/βcatenin signalling (Lin J. et al, 2017).

Coscio A. et al, demonstrated that miR-SNP (rs10898564) of FZD4 is most significantly associated with increased recurrence and death risk in NSCLC patients treated with only surgery but not in patients treated with surgery and chemotherapy. These reports suggest a potential role of FZD4-SNPs as predictive biomarkers for both recurrence and survival in early stage NSCLC patients.

Prostate cancer

In prostate cancer cells have been shown activation of Wnt signalling through FZD4 leading to epithelial-to-mesenchymal transition (EMT) and loss of cell adhesion (Gupta S. et al., 2010; Acevedo VD et al., 2007).

Breast cancer

Recently Lazzaroni F. et al. evidenced an autocrine activation of Wnt signalling in breast cancer cell line model. In MCF7 cell line model they identified the WNT10B/FZD4 interacting complex using the in situ proximity ligation assay and a dose dependent reduction of WNT10B/FZD4 complex after the treatment with pharmacological inhibitor of porcupine, a membrane-bound acyltransferase that is essential to the production of Wnt proteins.

Liver cancer

It was revealed that Let7b microRNA inhibit Wnt/β-catenin signaling pathway via downregulation of FZD4 in liver cancer cell, resulting in a reduction of proliferation, invasion, migration of liver cancer cells and reduction in the amount of cancer stem cells in liver (Cai H.et al 2017).

Glioblastoma

Microarray analysis in U87R4 invasive glioblastoma cell line reported an overexpression of FZD4, which actives Wnt/β catenin signalling pathway and promotes stemness and invasiveness of glioblastoma cells. (Jin X. et al. 2011).

Medulloblastoma

Recently evidences showed an involvement of Norrin/FZD4 signaling pathway in the cerebellar tumor medulloblastoma (MB) initiation. In this tumor, Norrin/FZD4 pathway acts as anti-tumor signal in the preneoplastic niche, in fact loss of function of Norrin/FZD4 signaling in the endothelian cells promotes the formation of preneoplastic lesion of MB and their progression to malignancies (Bassett E. et al., 2016).

Bladder cancer

FZD4 is a target of miR-493 in the bladder cancer. It was observed a down-regulated expression of miR-493 in the bladder cancer tissue in comparison with normal bladder tissue. MIR493 transfection in the T24 or J82 bladder cancer cell line inhibits FZD4 and Rho4 expression, resulting in the inhibition of cell motility and migration

These results, suggested that miR-493 represent a new tumor suppressor in the bladder cancer (Ueno K. et al., 2012).

Melanoma

It was reported that in melanoma cells Wnt signalling activation through FZD4 promotes tumor cell invasion and metastasis. WNT5a binds FZD4/LRP6 receptor complex and actives the guanosine triphosphatase adenosine diphosphate ribosylation factor 6 (ARF6), leading to the disruption of N-cadherin-βcatenin complex and accumulation of nuclear βcatenin, which increases the transcription of its target genes and stimulates melanoma invasion (Grossman A. et al., 2013)

Chronic Myeloid Leukemia

Agarwal P. et al., revealed a role of FZD4 in Wnt-mediated regulation of CML progenitor growth and their resistance to tyrosine kinase inhibitor (TKI) treatment. Silencing of FZD4 expression in combination with Nilotinib (NIL) treatment reduces Wnt signalling activation and the colony forming capacity of CML cells.

Colorectal cancer

Expression of FZD4 in colorectal cancer and its binding with the Norrin ligand, produced by the same cells and endothelial tumor cells, activates β-catenin signalling and regulates angiogenesis in the colorectal cancer microenvironment (K. Platinus et al. 2014).

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